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Candida krusei, a Multidrug-Resistant Opportunistic Fungal Pathogen: Geographic and Temporal Trends from the ARTEMIS DISK Antifungal Surveillance Program, 2001 to 2005[▽]

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***Candida krusei* is well known as a fungal pathogen for patients with hematologic malignancies and for transplant recipients. Using the ARTEMIS Antifungal Surveillance Program database, we describe geographic and temporal trends in the isolation of *C. krusei* from clinical specimens and the in vitro susceptibilities of 3,448 isolates to voriconazole as determined by CLSI (formerly NCCLS) disk diffusion testing. In addition, we report the in vitro susceptibilities of bloodstream infection isolates of *C. krusei* to amphotericin B (304 isolates), flucytosine (254 isolates), anidulafungin (121 isolates), caspofungin (300 isolates), and micafungin (102 isolates) as determined by CLSI broth microdilution methods. Geographic differences in isolation were apparent; the highest frequency of isolation was seen for the Czech Republic (7.6%) and the lowest for Indonesia, South Korea, and Thailand (0 to 0.3%). Overall, 83% of isolates were susceptible to voriconazole, ranging from 74.8% in Latin America to 92.3% in North America. *C. krusei* was most commonly isolated from hematology-oncology services, where only 76.7% of isolates were susceptible to voriconazole. There was no evidence of increasing resistance of *C. krusei* to voriconazole from 2001 to 2005. Decreased susceptibilities to amphotericin B (MIC at which 90% of isolates were inhibited [MIC_{90}], 4 μg/ml) and flucytosine (MIC_{90}, 16 μg/ml) were noted, whereas 100% of isolates were inhibited by ≤2 μg/ml of anidulafungin (MIC_{90}, 0.06 μg/ml), micafungin (MIC_{90}, 0.12 μg/ml) or caspofungin (MIC_{90}, 0.25 μg/ml). *C. krusei* is an uncommon but multidrug-resistant fungal pathogen. Among the systemically active antifungal agents, the echinocandins appear to be the most active against this important pathogen.**

Candida krusei has been recognized as a potentially multidrug-resistant (MDR) fungal pathogen, due to its intrinsic fluconazole resistance combined with reports of decreased susceptibility to both flucytosine and amphotericin B (1, 2, 3, 6, 20, 22, 23, 26, 37, 39, 47, 61). Several authors have reported breakthrough infections due to *C. krusei* among patients receiving fluconazole or amphotericin B (1, 11, 19, 21, 31, 34, 61), and Goldman et al. (9) found that response rates of *C. krusei* infection were significantly better for patients who had received amphotericin B in doses of ≥1 mg/kg of body weight per day than for those who had received lower doses. Furthermore, amphotericin B exhibits markedly delayed killing kinetics against *C. krusei* compared with that against *Candida albicans* (4, 19).

The MDR phenotype exhibited by *C. krusei* poses a therapeutic dilemma when one is considering treatment choices for neutropenic and critically ill patients, especially for those with prior exposure to fluconazole (32, 54, 56, 57). Despite intrinsic resistance to fluconazole, *C. krusei* usually remains susceptible in vitro to voriconazole due to the more effective binding of voriconazole to the cytochrome P-450 isoenzyme of *C. krusei* (7, 48). Furthermore, voriconazole has been used successfully to treat some patients infected with *C. krusei* (16, 29). In addition, the echinocandins have been used based on their fungicidal activity and excellent in vitro activity against *C. krusei* (41, 42, 56, 57). Whereas echinocandin antifungals such as caspofungin have been used successfully to treat several different infections involving *C. krusei* (21, 28, 31, 34, 50), there have been recent troubling reports of caspofungin failure in the treatment of *C. krusei* infections (10, 15, 33). Notably, Hakki et al. (10) reported a strain of *C. krusei* from a leukemic patient that displayed reduced susceptibilities to caspofungin, anidulafungin, and micafungin. The strain emerged during therapy with caspofungin and subsequently was shown to contain a heterozygous mutation in the *FKS1* gene resulting in altered sensitivity of the glucan synthesis enzyme complex to inhibition by echinocandin drugs (15). These findings emphasize the plasticity of *C. krusei* with respect to the development of resistance to a broad array of antifungals. Along with *Candida glabrata*, *C. krusei* must be considered an important indicator species that should be monitored for the development of antifungal resistance (15, 47).

Despite the MDR phenotype exhibited by *C. krusei*, few studies have addressed the global epidemiology and antifungal susceptibility profile of *C. krusei* (23). Most of the available information regarding *C. krusei* comes from single institutions

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(1) or represents a limited geographic region (23). In the current study, we use the extensive database provided by the ARTEMIS DISK Antifungal Surveillance Program (49) to describe geographic and temporal trends in the isolation of *C. krusei* from clinical specimens collected from 124 medical centers between 2001 and 2005, as well as the in vitro susceptibilities of 3,448 clinical isolates, including 326 bloodstream infection (BSI) isolates, of this species to voriconazole, as determined by standardized disk diffusion testing. The in vitro susceptibilities of BSI isolates to amphotericin B, flucytosine, anidulafungin, caspofungin, and micafungin were also determined using either Etest (for amphotericin B; AB Biodisk, Solna, Sweden) or Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) broth microdilution methods. This report will serve as the largest study of *C. krusei* isolates to date.

MATERIALS AND METHODS

Organisms and test sites. A total of 137,487 isolates of *Candida* spp., including 3,448 isolates of *C. krusei* from 124 different medical centers in the Asia-Pacific region (23 sites), Latin America (16 sites), Europe (64 sites), the Africa/Middle East region (11 sites), and North America (10 sites) were collected and tested against voriconazole between January 2001 and December 2005. All *Candida* spp. considered pathogens from all body sites (e.g., blood, normally sterile body fluids [NSBF], deep tissue, genital tract, urine, respiratory tract, skin and soft tissue) and isolates from all in-hospital and outpatient locations during the study period from 2001 through 2005 were tested. Of the 326 BSI isolates of *C. krusei* collected, 304 were sent to the University of Iowa for testing against amphotericin B and other antifungal agents.

Data for *C. krusei* were stratified by year of isolation, geographic region, clinical service (hospital location), and specimen type. *Candida* spp. considered by the local site investigator to be colonizers, that is, not associated with pathology, were excluded, as were duplicate isolates (the same species and the same susceptible-resistant biotype profile within any 7-day period). Isolates were identified in accordance with each site's routine methods (49).

Susceptibility test methods. Disk diffusion testing of voriconazole was performed as described previously (49) and in accordance with CLSI document M44-A (25). Agar plates (diameter, 90, 100, or 150 mm) containing Mueller-Hinton agar (obtained locally at all sites) supplemented with 2% glucose and 0.5 μg of methylene blue per ml at a depth of 4.0 mm were used. The agar surface was inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of a 0.5 McFarland standard. Voriconazole (1 μg) disks (Becton Dickinson, Sparks, MD) were placed on the surfaces of the inoculated plates, and the plates were incubated in air at 35 to 37°C and read at 18 to 24 h. Zone diameter end points were read at 80% growth inhibition by using a BIOMIC image analysis plate reader system (Giles Scientific, Santa Barbara, CA) (49).

MICs of flucytosine, anidulafungin, caspofungin, and micafungin were determined by broth microdilution as described previously (36, 41–43). All isolates were tested in RPMI broth with a 24-h (anidulafungin, caspofungin, and micafungin) or 48-h (flucytosine) incubation and an end point criterion of a prominent reduction in growth relative to that of the control (represented by ≥50% growth inhibition). The susceptibilities of *C. krusei* isolates to amphotericin B were determined by using Etest (AB Biodisk) as described previously (38).

The interpretive criteria for the voriconazole disk diffusion tests were those of the CLSI (44), as follows: susceptible (S), zone diameter of ≥17 mm; susceptible dose dependent (SDD), zone diameters of 14 to 16 mm; resistant (R), zone diameters of ≤13 mm. The corresponding MIC breakpoints (44) are as follows: S, MIC of ≤1 μg/ml; SDD, MIC of 2 μg/ml; R, MIC of ≥4 μg/ml.

The interpretive criteria for all three echinocandins were those recently assigned by the CLSI (minutes of June 2007 CLSI meeting). Isolates for which the MIC is ≤2 μg/ml are designated S. A category of R has not been established for the echinocandins due to a paucity of "resistant" isolates treated with an echinocandin. Those isolates for which an echinocandin MIC is >2 μg/ml are to be designated "nonsusceptible."

The interpretive criteria for flucytosine were those recommended by the CLSI (24): S, MIC of ≤4 μg/ml; intermediate (I), MIC of 8 to 16 μg/ml; R, MIC of ≥32 μg/ml. Interpretive breakpoints have not been established for amphotericin B.

QC. Quality control (QC) was performed in accordance with CLSI documents M44-A (voriconazole) and M27-A2 (all other agents) by using *Candida albicans* ATCC 90029, *Candida parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258 (24, 25). More than 99% of QC results were within the acceptable limits.

Analysis of results. All disk zone diameters were read by electronic image analysis and interpreted and recorded with the BIOMIC plate reader system (Giles). Test results were sent by e-mail to Giles Scientific for analysis. The zone diameter, susceptibility category (S, SDD, or R), and QC test results were all recorded electronically. Patient and doctor names, duplicate test results (same patient, same species, and same biotype results), and uncontrolled results were automatically eliminated by the BIOMIC system prior to analysis. In the present study, voriconazole S, SDD, and R results for *C. krusei* were stratified by year of collection, geographic region, clinical specimen type, and hospital location. The chi-square test, with Yates' correction, was used to determine the statistical significance of differences in voriconazole isolation or susceptibility according to other categorical variables. Alpha was set at 0.05, and all reported *P* values are two-tailed.

RESULTS

Isolation rates of *C. krusei* over time and by geographic region. A total of 137,487 isolates of *Candida* spp. were recovered and identified at 124 study sites between January 2001 and December 2005 (49). *C. krusei* ranked fifth among 22 different species of *Candida*, accounting for 2.5% of all isolates (Table 1). The frequency of isolation of *C. krusei* did not change (range, 2.3 to 2.7%) over the course of the study.

C. krusei represented 3.3% of all *Candida* spp. isolated in both Europe and North America (3.5% in the United States, 1.8% in Canada) (Table 1). In Europe, *C. krusei* was isolated most frequently (≥5% of all *Candida* sp. isolates) in the Eastern European countries of the Czech Republic (7.6%), Poland (6.0%), and Slovakia (5.1%) and was distinctly uncommon (<1%) in The Netherlands (0.5%). *C. krusei* was also quite uncommon in the Asia-Pacific region (1.3%) and Latin America (1.7%). Fewer than 1% of all *Candida* strains isolated in Indonesia (0%), South Korea (0.3%), Taiwan (0.6%), Thailand (0.3%), and Ecuador (0.5%) were identified as *C. krusei* (Table 1).

Geographic differences in the susceptibility of *C. krusei* to voriconazole. Table 1 presents the in vitro susceptibility of *C. krusei* to voriconazole stratified by country and geographic region of origin, as determined by CLSI disk diffusion testing. Overall, *C. krusei* exhibited decreased susceptibility to voriconazole (82.9% S, 7.8% R) compared to that of *C. albicans* (98.4% S, 1.2% R) (data not shown).

Considerable differences in the susceptibility of *C. krusei* to voriconazole were observed across the five broad regions: isolates from North America were the most susceptible (92.3% S, 4.3% R), while the lowest overall susceptibility was seen among isolates from Latin America (74.8% S, 16.0% R; $P < 0.001$ for the difference between North America and Latin America in the proportion of *C. krusei* isolates that were susceptible to voriconazole). The lowest susceptibilities to voriconazole (<70%) were seen in the Latin American countries of Brazil (65.9% S, 34.1% R), Colombia (61.8% S, 18.2% R), and Mexico (63.6% S, 36.4% R). No other country reported susceptibility rates of less than 70%. In contrast, susceptibility rates exceeded 90% in 14 countries: Australia (100%), Taiwan (94.7%), Thailand (100%), Belgium (97.3%), Germany (90.9%), The Netherlands (100%), Poland (98.4%), Portugal (96.1%), Slovakia (90.1%), Switzerland (93.6%), Argentina (93.8%), Israel (94.7%), Canada (93.8%), and the

TABLE 1. Geographic differences in the frequency of isolation and in vitro susceptibility of *Candida krusei* to voriconazole[a]

Region and country	Total no. of *Candida* isolates	Total no. (%) of *C. krusei* isolates	% of *C. krusei* isolates in the following category:		
			S	SDD	R
Asia-Pacific	26,580	350 (1.2)	83.7	10.0	6.3
Australia	731	27 (3.7)	100.0		
China	7,663	142 (1.9)	83.8	7.0	9.2
India	356	8 (2.2)	87.5	12.5	
Indonesia	10	0 (0.0)			
Malaysia	10,510	142 (1.3)	78.9	16.2	4.9
South Korea	3,515	10 (0.3)	80.0	10.0	10.0
Taiwan	3,083	19 (0.6)	94.7		5.3
Thailand	632	2 (0.03)	100.0		
Europe	75,594	2.459 (3.3)	82.1	10.1	7.8
Belgium	5,213	182 (3.5)	97.3	1.6	1.1
Czech Republic	6,541	498 (7.6)	74.9	15.1	10.0
France	2,363	57 (2.4)	78.9	12.3	8.8
Germany	2,489	110 (4.4)	90.9	4.5	4.5
Greece	589	15 (2.5)	80.0		20.0
Hungary	12,655	519 (4.1)	70.9	17.9	11.2
Italy	5,172	177 (3.4)	89.8	5.1	5.1
The Netherlands	6,422	31 (0.5)	93.5	3.2	3.2
Norway	253	6 (2.4)	66.7	33.2	
Poland	1,022	61 (6.0)	98.4		1.6
Portugal	2,843	51 (1.8)	96.1	3.9	
Russia	5,965	203 (3.4)	86.7	7.4	5.9
Slovakia	3,559	182 (5.1)	90.1	5.5	4.4
Spain	6,328	126 (2.0)	77.0	8.7	14.3
Switzerland	1,706	47 (2.8)	93.6	4.3	2.1
Turkey	1,320	28 (2.1)	89.3	3.6	7.1
United Kingdom	11,154	166 (1.5)	81.9	7.8	10.2
Latin America	19,079	206 (1.1)	74.8	9.2	16.0
Argentina	6,347	61 (1.0)	93.8	4.7	1.6
Brazil	3,764	41 (1.1)	65.9		34.1
Colombia	3,679	55 (1.5)	61.8	20.0	18.2
Ecuador	2,607	13 (0.5)	76.9	15.4	7.7
Mexico	889	11 (1.2)	63.6		36.4
Venezuela	1,793	22 (1.2)	72.7	13.6	13.6
Africa/Middle East	6,452	108 (1.7)	88.0	6.5	5.5
South Africa	5,286	84 (1.6)	86.9	7.1	6.0
Israel	814	19 (2.3)	94.7	5.3	
Saudi Arabia	352	5 (1.4)	80.0		20.0
North America	9,782	325 (3.3)	92.3	3.4	4.3
Canada	913	16 (1.8)	93.8	6.3	
United States	8,869	309 (3.5)	92.2	3.2	4.5
Total	137,487	3,448 (2.5)	82.9	9.3	7.8

[a] Isolates were obtained from 124 institutions. Voriconazole disk testing was performed in accordance with CLSI document M44-A (25). The interpretive breakpoints (zone diameters) were as follows: susceptible (S), ≥17 mm; susceptible dose dependent (SDD), 14 to 16 mm; resistant (R), ≤13 mm.

United States (92.2%). These extreme differences in the susceptibility of *C. krusei* to voriconazole are important to understand and monitor, and they emphasize the importance of antifungal susceptibility testing of this species if voriconazole is considered a therapeutic option.

Trends in resistance to voriconazole among *C. krusei* isolates over time. There was no evidence of increasing resistance to voriconazole among *C. krusei* isolates tested between 2001 and 2005. Resistance to voriconazole ranged from 8.0% in 2001 to 7.9% in 2005 (overall range, 6.1 to 8.3) (data not shown).

TABLE 2. Susceptibility of *Candida krusei* to voriconazole by clinical service

Clinical service (total no. of *Candida* isolates)	No. of *C. krusei* isolates	% *C. krusei* isolates[a]	% of *C. krusei* isolates in the following category:		
			S	SDD	R
Hematology-oncology (8,262)	514	6.2	76.7	13.4	9.9
Medical (32,872)	752	2.3	82.7	8.4	8.9
Surgical (8,673)	218	2.5	82.6	10.1	7.3
Intensive care unit (18,215)	445	2.4	81.8	11.0	7.2
Dermatology (2,450)	25	1.0	68.0	24.0	8.0
ObGyn (17,013)	220	1.3	77.3	14.5	8.2
Urology (1,270)	26	2.0	73.1	15.4	11.5
Outpatient (11,438)	149	1.3	81.2	7.4	11.4
Other, NOS (37,294)	1,099	2.9	88.5	5.9	5.6

[a] *C. krusei* isolates as a percentage of all *Candida* isolates from the indicated clinical service.

Differences in the frequency of isolation and the voriconazole susceptibility profile of *C. krusei* by clinical service. The clinical services reporting the isolation of *C. krusei* from patient specimens included the hematology-oncology service, medical and surgical services, intensive care units (medical, surgical, and neonatal), the dermatology service, the obstetrics and gynecology (ObGyn) service, the urology service, and the outpatient service (Table 2). Those strains from services with only a few isolates and those for which a clinical service was not specified were included in the category "other, not otherwise specified" (other, NOS).

As expected, *C. krusei* represented a higher proportion of *Candida* strains isolated from patients hospitalized in hematology-oncology services than from all other services combined (6.2% versus 2.3%; $P < 0.001$). *C. krusei* was especially uncommon among *Candida* isolates from the dermatology, ObGyn, and outpatient services. Voriconazole was least active against isolates from the dermatology (68.0%) and urology (73.1%) services and most active against isolates from the medical (82.7%) and surgical (82.6%) services and from the unspecified (other, NOS) group (88.5%). Fewer than 80% of isolates from the hematology-oncology service were susceptible to voriconazole (76.7%).

Differences in the frequency of isolation and the voriconazole susceptibility profile of *C. krusei* by clinical specimen type. The major specimen types yielding *C. krusei* as a putative pathogen included blood, NSBF, urine, respiratory, general, and skin/soft tissue specimens (Table 3). Those isolates from uncommon specimen types and those for which a specimen type was not recorded were grouped under the category "miscellaneous, NOS."

C. krusei was isolated from 2 to 3% (each) of blood, NSBF, urine, respiratory, and skin/soft tissue specimens. It was isolated infrequently from genital specimens. Interestingly, *C. krusei* isolates from blood were more likely to be susceptible to voriconazole than those from urine (89.0 versus 76.6%, respectively; $P < 0.001$). This pattern was similar to that reported previously for another uncommon species of *Candida*, *Candida guilliermondii* (45).

TABLE 3. Susceptibility of *Candida krusei* to voriconazole by specimen type

Specimen type or site (total no. of *Candida* isolates)	No. of *C. krusei* isolates	% *C. krusei* isolates[a]	% of *C. krusei* isolates in the following category:		
			S	SDD	R
Blood (14,583)	326	2.2	89.0	3.7	7.4
NSBF (5,940)	151	2.5	81.5	11.9	6.6
Urine (17,693)	368	2.1	76.6	12.0	11.4
Respiratory (38,578)	1,164	3.0	81.4	10.0	8.6
Genital (30,009)	426	1.4	81.5	10.6	8.0
Skin/soft tissue (8,078)	178	2.2	85.4	7.9	6.7
Misc.,[b] NOS (22,606)	835	3.7	86.0	8.6	5.4

[a] *C. krusei* isolates as a percentage of all isolates from the indicated body site or specimen type.
[b] Misc., miscellaneous.

Activities of amphotericin B, flucytosine, and the echinocandins against bloodstream isolates of *C. krusei*. Among the 326 BSI isolates of *C. krusei* collected during this survey, 304 isolates were sent to the University of Iowa for further testing against amphotericin B (304 isolates), flucytosine (254 isolates), anidulafungin (121 isolates), caspofungin (300 isolates), and micafungin (102 isolates) (Table 4). Our broth dilution antifungal susceptibility testing panels changed during the 5-year span of the study, which explains why the numbers of isolates tested against each of the agents differ somewhat (e.g., anidulafungin and micafungin were added to the panel, and flucytosine was dropped, in the latter years of the study).

Among the BSI isolates tested, decreased susceptibilities to amphotericin B (MIC at which 90% of isolates were inhibited [MIC_{90}], 4 μg/ml) and flucytosine (MIC_{90}, 16 μg/ml; 8% S) were noted. By comparison, the MIC_{90}s of amphotericin B and flucytosine tested against *C. albicans* were 0.5 μg/ml and 1.0 μg/ml, respectively (data not shown). All isolates of *C. krusei* were susceptible to the three echinocandins at the CLSI breakpoint concentration of ≤2 μg/ml: MIC_{90}s were 0.06 μg/ml for anidulafungin, 0.12 μg/ml for micafungin, and 0.25 μg/ml for caspofungin.

DISCUSSION

The results from this extensive survey of *C. krusei* both confirm and extend previous observations concerning this species (1, 3, 6, 22, 23, 39, 40, 47, 52). *C. krusei* remains a relatively uncommon clinical isolate throughout the world (Table 1). Most notable is the very low frequency of isolation in both the Asia-Pacific and Latin American regions as opposed to the higher frequency observed in several Eastern European countries. This could represent geographic differences in the ecology of *Candida* species or in the use of cytotoxic drugs and antimicrobial agents (22). *C. krusei* is most common among patients with hematologic malignancies and recipients of blood and marrow transplants (1, 2, 12, 20, 26, 61). Whether this observation is a direct result of fluconazole administration remains controversial, since others have reported infections due to this species before the introduction of fluconazole (14, 22, 60). In addition, several centers have reported no increased incidence of infections with *C. krusei*, despite the widespread use of fluconazole (8, 17, 18, 51, 55). As reported in several smaller studies (5, 6, 10, 23, 30, 34, 37, 39, 55), *C. krusei* was generally susceptible to voriconazole, although considerable geographic differences were seen (Table 1), like those seen with *C. glabrata* (49) and *Candida rugosa* (46).

There was less variability in voriconazole susceptibility across the different clinical services (Table 2) and specimen types (Table 3). Notably, BSI isolates of *C. krusei* exhibited the greatest susceptibility to voriconazole. Although isolates of *C. krusei* from blood and NSBF are clearly pathogenic, the isolation of this organism from nonsterile sites (e.g., urine, respiratory, and genital specimens) may simply represent colonization rather than infection. That said, colonization with *C. krusei* precedes infection in approximately 70% of patients (1, 9, 13, 26, 35, 53, 59), and colonizing strains of *C. krusei* have been shown to be indistinguishable from BSI isolates obtained from the same patient, supporting the role of this species as an endogenous pathogen (3, 27, 58). Thus, the isolation of *C. krusei* from nonsterile sites may have direct bearing on the selection of antifungal therapy.

We document a pattern of decreased susceptibility of *C. krusei* to amphotericin B and flucytosine that, along with intrinsic resistance to fluconazole, results in an MDR phenotype. As seen previously (41, 43), the echinocandins were all active against BSI isolates of *C. krusei.* The activity of this class of antifungal agents against this MDR pathogen is encouraging; however, the reports of resistance developing to caspofungin during the treatment of *C. krusei* infection must be kept in mind. The reduced susceptibility to caspofungin in both cases was associated with the onset of clinically apparent fungal infection involving anatomic sites, such as the eye (10) or the central nervous system (33), where adequate free drug levels cannot be readily obtained. In such instances, the availability of an agent such as voriconazole, with both activity against the infecting organism and good penetration into ocular and cen-

TABLE 4. In vitro activities of amphotericin B, flucytosine, and the echinocandins against bloodstream isolates of *Candida krusei*

Antifungal agent[a]	No. of isolates tested	Cumulative % of *C. krusei* isolates inhibited at a MIC (μg/ml) of:											
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Amphotericin B	304	4	4	5	7	24	51	85	98	99	100		
Flucytosine	254		1	1	1	1	2	5	8	26	93	99	99
Anidulafungin	121	49	92	99	99	100							
Caspofungin	300	1	40	69	90	98	99	100					
Micafungin	102	12	84	99	100								

[a] Amphotericin B MICs were determined by Etest after 24 h of incubation. Echinocandin MICs were determined using RPMI 1640 broth with 24 h of incubation and an end point criterion of a prominent reduction in growth (MIC-2).

tral nervous system sites, may be vital to a successful outcome (33). Continued monitoring of the susceptibility of *C. krusei* to voriconazole and the echinocandins is clearly warranted.

In summary, we have used data from the ARTEMIS DISK Antifungal Surveillance Program (49) to increase our understanding of *C. krusei* as an opportunistic fungal pathogen. Our findings demonstrate considerable geographic diversity both in its occurrence and in its susceptibility to the expanded-spectrum triazole voriconazole. In addition to resistance to fluconazole, this species clearly exhibits decreased susceptibility to amphotericin B and flucytosine. Given the variable activity of voriconazole against this species, demonstrated here, and recent reports of acquired resistance to echinocandins, testing of the susceptibility of *C. krusei* to these potentially useful antifungal agents may be warranted to help guide therapeutic decisions.

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REFERENCES

1. **Abbas, J., G. P. Bodey, H. A. Hanna, M. Mardani, E. Girgawy, D. Abi-Said, E. Whimbey, R. Hachem, and I. Raab.** 2000. *Candida krusei* fungemia: an escalating serious infection in immunocompromised patients. Arch. Intern. Med. **160:**2659–2664.
2. **Abi-Said, D., E. Anaissie, O. Uzum, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin. Infect. Dis. **24:**1122–1128.
3. **Berrouane, Y. F., R. J. Hollis, and M. A. Pfaller.** 1996. Strain variation among and antifungal susceptibilities of isolates of *Candida krusei.* J. Clin. Microbiol. **34:**1856–1858.
4. **Cantón, E., J. Peman, M. Gobernado, A. Viudes, and A. Espinel-Ingroff.** 2004. Patterns of amphotericin B killing kinetics against seven *Candida* species. Antimicrob. Agents Chemother. **48:**2477–2482.
5. **Cuenca-Estrella, M., A. Gomez-Lopez, E. Mellado, M. J. Bintrago, A. Mongon, and J. L. Rodriguez-Tudela.** 2006. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. Antimicrob. Agents Chemother. **50:**917–921.
6. **Drago, M., M. M. Scaltrio, G. Morace, and the GISIA-2 Group.** 2004. In vitro activity of voriconazole and other antifungal agents against clinical isolates of *Candida glabrata* and *Candida krusei.* Eur. J. Clin. Microbiol. Infect. Dis. **23:**619–624.
7. **Fukuoka, T., D. A. Johnston, C. A. Winslow, M. J. deGroot, C. Burt, C. A. Hitchcock, and S. G. Filler.** 2003. Genetic basis for differential activities of fluconazole and voriconazole against *Candida krusei.* Antimicrob. Agents Chemother. **47:**1213–1219.
8. **Girmenia, C., L. Pagano, G. Leona, and P. Martino.** 2001. Fluconazole and *Candida krusei* fungemia. Arch. Intern. Med. **161:**2267–2269.
9. **Goldman, M., J. C. Pottage, and D. C. Weaver.** 1993. *Candida krusei* fungemia. Report of 4 cases and review of the literature. Medicine **72:**143–150.
10. **Hakki, M., J. F. Staab, and K. A. Marr.** 2006. Emergence of a *Candida krusei* isolate with reduced susceptibility to caspofungin during therapy. Antimicrob. Agents Chemother. **50:**2522–2524.
11. **Hepburn, M. J., G. J. Pennick, D. A. Sutton, G. E. Crawford, and J. H. Jorgenson.** 2003. *Candida krusei* renal cyst infection and measurement of amphotericin B levels in cystic fluid in a patient receiving AmBisome. Med. Mycol. **41:**163–165.
12. **Hope, W., A. Morton, and D. P. Eisen.** 2002. Increase in prevalence of

nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. J. Hosp. Infect. **50:**56–65.
13. **Horn, R., B. Wong, T. E. Kiehn, and D. Armstrong.** 1985. Fungemia in a cancer hospital: changing frequency, earlier onset, and results of therapy. Rev. Infect. Dis. **7:**646–655.
14. **Iwen, P. C., D. M. Kelly, E. C. Reed, and S. H. Hinrichs.** 1995. Invasive infection due to *Candida krusei* in immunocompromised patients not treated with fluconazole. Clin. Infect. Dis. **20:**342–347.
15. **Kahn, J. N., G. Garcia-Effron, M. J. Hsu, S. Park, K. A. Marr, and D. S. Perlin.** 2007. Acquired echinocandin resistance in a *Candida krusei* isolate due to modification of glucan synthase. Antimicrob. Agents Chemother. **51:**1876–1878.
16. **Kullberg, B. J., J. D. Sobel, M. Rhunke, P. G. Pappas, C. Viscoli, J. H. Rex, J. D. Cleary, E. Rubenstein, L. W. P. Church, J. M. Brown, H. T. Schlamm, I. T. Oborska, F. Hilton, and M. R. Hodges.** 2005. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidemia in non-neutropenic patients: a randomized non-inferiority trial. Lancet **366:**1435–1442.
17. **Kunova, A., J. Trupi, A. Demitrovicova, et al.** 1997. Eight-year surveillance of non-*albicans Candida* after fluconazole had been introduced into antifungal prophylaxis. Microb. Drug Resist. **3:**283–287.
18. **Lin, M. Y., Y. Carmeli, J. Zumsteg, E. L. Flores, J. Tolentino, P. Sreeramoju, and S. G. Weber.** 2005. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. Antimicrob. Agents Chemother. **49:**4555–4560.
19. **Majoros, L., I. Szegedi, G. Kardos, C. Erdesz, J. Konya, and C. Kiss.** 2006. Slow response of invasive *Candida krusei* infection to amphotericin B in a clinical time-kill study. Eur. J. Clin. Microbiol. Infect. Dis. **25:**803–806.
20. **Marr, K. A., K. Seidel, T. C. White, and R. A. Bowden.** 2000. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J. Infect. Dis. **181:**309–316.
21. **McGee, W. T., and G. J. Tereso.** 2003. Successful treatment of *Candida krusei* infection with caspofungin acetate: a new antifungal agent. Crit. Care Med. **31:**1577–1578.
22. **Merz, W. G., J. E. Karp, D. Schron, and R. Saral.** 1986. Increased incidence of fungemia caused by *Candida krusei*. J. Clin. Microbiol. **24:**581–584.
23. **Muñoz, P., M. Sanchez-Somolinos, L. Alcala, M. Rodriguez-Creixems, T. Pelaez, and E. Bouza.** 2005. *Candida krusei* fungemia: antifungal susceptibility and clinical presentation of an uncommon entity during 15 years in a single general hospital. J. Antimicrob. Chemother. **55:**188–193.
24. **National Committee for Clinical Laboratory Standards.** 2002. Reference method for broth dilution antifungal susceptibility testing of yeasts: approved standard, 2nd ed., M27–A2. National Committee for Clinical Laboratory Standards, Wayne, PA.
25. **National Committee for Clinical Laboratory Standards.** 2004. Methods for antifungal disk diffusion susceptibility testing of yeasts: approved guideline, M44-A. National Committee for Clinical Laboratory Standards, Wayne, PA.
26. **Nguyen, M. H., J. E. Peacock, Jr., A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. **100:**617–623.
27. **Noskin, G. A., J. Lee, D. M. Hacek, M. Postelnick, B. E. Reisberg, V. Stosor, S. A. Weitzman, and L. R. Peterson.** 1996. Molecular typing for investigating an outbreak of *Candida krusei*. Diagn. Microbiol. Infect. Dis. **26:**117–123.
28. **Olver, N. J., F. Scott, and G. S. Shankland.** 2006. Successful treatment of *Candida krusei* fungemia with amphotericin B and caspofungin. Med. Mycol. **44:**655–657.
29. **Ostrosky-Zeichner, L., A. M. L. Oude Lashof, B. J. Kullberg, and J. H. Rex.** 2003. Voriconazole salvage treatment of invasive candidiasis. Eur. J. Clin. Microbiol. Infect. Dis. **22:**651–655.
30. **Ostrosky-Zeichner, L., J. H. Rex, P. G. Pappas, R. J. Hamill, R. A. Larsen, H. W. Horowitz, W. G. Powderly, N. Hyslop, C. A. Kauffman, J. Clearly, J. E. Mangino, and J. Lee.** 2003. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. Antimicrob. Agents Chemother. **47:**3149–3154.
31. **Pan, S. C., S. M. Hsieh, S. C. Chang, H. T. Lee, and Y. C. Chen.** 2005. Septic *Candida krusei* thrombophlebitis of inferior vena cava with persistent fungemia successfully treated by new antifungal agents. Med. Mycol. **43:**731–734.
32. **Pappas, P. G., J. H. Rex, J. D. Sobel, S. G. Filler, W. E. Dismukes, T. J. Walsh, and J. E. Edwards for the Infectious Diseases Society of America.** 2004. Guidelines for treatment of candidiasis. Clin. Infect. Dis. **38:**161–189.
33. **Pelletier, R., I. Alarie, R. Lagace, and T. J. Walsh.** 2005. Emergence of disseminated candidiasis caused by *Candida krusei* during treatment with caspofungin: case report and review of literature. Med. Mycol. **43:**559–564.
34. **Pemán, J., I. Jarque, M. Bosch, E. Canton, M. Salavert, R. de Llanos, and A. Molina.** 2006. Spondylodiscitis caused by *Candida krusei*: case report and susceptibility patterns. J. Clin. Microbiol. **44:**1912–1914.
35. **Pfaller, M., I. Cabezudo, F. Koontz, M. Bale, and R. Gingrich.** 1987. Predictive value of surveillance cultures for systemic infection due to *Candida* species. Eur. J. Clin. Microbiol. **6:**628–633.
36. **Pfaller, M. A., S. A. Messer, L. Boyken, H. Huynh, R. J. Hollis, and D. J. Diekema.** 2002. In vitro activities of 5-fluorocytosine against 8,803 clinical isolates of *Candida* spp.: global assessment of primary resistance using National Committee for Clinical Laboratory Standards susceptibility testing methods. Antimicrob. Agents Chemother. **46:**3518–3521.
37. **Pfaller, M. A., D. J. Diekema, S. A. Messer, L. Boyken, R. J. Hollis, R. N. Jones, and the International Fungal Surveillance Participant Group.** 2003. In vitro activities of voriconazole, posaconazole, and four licensed systemic antifungal agents against *Candida* species infrequently isolated from blood. J. Clin. Microbiol. **41:**78–83.
38. **Pfaller, M. A., L. Boyken, S. A. Messer, S. Tendolkar, R. J. Hollis, and D. J. Diekema.** 2004. Evaluation of the Etest method using Mueller-Hinton agar with glucose and methylene blue for determining amphotericin B MICs for 4,936 clinical isolates of *Candida* species. J. Clin. Microbiol. **42:**4977–4979.
39. **Pfaller, M. A., and D. J. Diekema.** 2004. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*. J. Clin. Microbiol. **42:**4419–4431.
40. **Pfaller, M. A., and D. J. Diekema.** 2004. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. Clin. Microbiol. Infect. **10**(Suppl. 1)**:**11–23.
41. **Pfaller, M. A., L. Boyken, R. J. Hollis, S. A. Messer, S. Tendolkar, and D. J. Diekema.** 2005. In vitro activities of anidulafungin against more than 2,500 clinical isolates of *Candida* spp., including 315 isolates resistant to fluconazole. J. Clin. Microbiol. **43:**5425–5427.
42. **Pfaller, M. A., L. Boyken, R. J. Hollis, S. A. Messer, S. Tendolkar, and D. J. Diekema.** 2006. In vitro susceptibilities of *Candida* spp. to caspofungin: four years of global surveillance. J. Clin. Microbiol. **44:**760–763.
43. **Pfaller, M. A., L. Boyken, R. J. Hollis, S. A. Messer, S. Tendolkar, and D. J. Diekema.** 2006. Global surveillance of in vitro activity of micafungin: a comparison with caspofungin by CLSI-recommended methods. J. Clin. Microbiol. **44:**3533–3538.
44. **Pfaller, M. A., D. J. Diekema, J. H. Rex, A. Espinel-Ingroff, E. M. Johnson, D. Andes, V. Chaturvedi, M. A. Ghannoum, F. C. Odds, M. G. Rinaldi, D. J. Sheehan, P. Troke, T. J. Walsh, and D. W. Warnock.** 2006. Correlation of MIC with outcome for *Candida* species tested against voriconazole: analysis and proposal for interpretive breakpoints. J. Clin. Microbiol. **44:**819–826.
45. **Pfaller, M. A., D. J. Diekema, M. Mendez, C. Kibbler, P. Erzebert, S. C. Chang, D. L. Gibbs, V. A. Newell, and the Global Antifungal Surveillance Group.** 2006. *Candida guilliermondii*, an opportunistic fungal pathogen with decreased susceptibility to fluconazole: geographic and temporal trends from the ARTEMIS DISK Antifungal Surveillance Program. J. Clin. Microbiol. **44:**3551–3556.
46. **Pfaller, M. A., D. J. Diekema, A. L. Colombo, C. Kibbler, K. Peng, D. L. Gibbs, V. A. Newell, and the Global Antifungal Surveillance Group.** 2006. *Candida rugosa*, an emerging pathogen with resistance to azoles: geographic and temporal trends from the ARTEMIS DISK Antifungal Surveillance Program. J. Clin. Microbiol. **44:**3578–3582.
47. **Pfaller, M. A., and D. J. Diekema.** 2007. Epidemiology of invasive candidiasis: a persistent public health problem. Clin. Microbiol. Rev. **20:**133–163.
48. **Pfaller, M. A., and D. J. Diekema.** 2007. Azole antifungal drug cross-resistance: mechanisms, epidemiology, and clinical significance. J. Invasive Fungal Infect. **1:**74–93.
49. **Pfaller, M. A., D. J. Diekema, D. L. Gibbs, V. A. Newell, J. F. Meis, I. M. Gould, W. Fu, A. L. Colombo, E. Rodriguez-Noriega, and the Global Antifungal Surveillance Group.** 2007. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2005: an 8.5-year analysis of susceptibilities of *Candida* species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J. Clin. Microbiol. **45:**1735–1745.
50. **Rajendram, R., N. J. Alp, A. R. Mitchell, I. C. J. W. Bowler, and J. C. Forfar.** 2005. *Candida* prosthetic valve endocarditis cured by caspofungin therapy without valve replacement. Clin. Infect. Dis. **40:**e72–e74.
51. **Safdar, A., F. van Rhee, J. P. Henslee-Downey, S. Singhal, and J. Mehta.** 2001. *Candida glabrata* and *Candida krusei* fungemia after high-risk allogeneic marrow transplantation: no adverse effect of low-dose fluconazole prophylaxis on incidence and outcome. Bone Marrow Transplant. **28:**873–878.
52. **Samaranayake, Y. H., and L. P. Samaranayake.** 1994. *Candida krusei*: biology, epidemiology, pathogenicity and clinical manifestations of an emerging pathogen. J. Med. Microbiol. **41:**295–310.
53. **Sandford, G. R., W. G. Merz, J. R. Wingard, P. Charache, and R. Saral.** 1980. The value of fungal surveillance cultures as predictors of systemic fungal infections. J. Infect. Dis. **142:**503–509.
54. **Singh, S., J. D. Sobel, P. Bhargava, D. Boikov, and J. A. Vasquez.** 2002. Vaginitis due to *Candida krusei*: epidemiology, clinical aspects, and therapy. Clin. Infect. Dis. **35:**1066–1070.
55. **Slavin, M. A., B. Osbourne, R. Adams, et al.** 1995. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J. Infect. Dis. **171:**1545–1552.

56. **Spanakis, E. K., G. Aperis, and E. Mylonakis.** 2006. New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage. Clin. Infect. Dis. **43:**1060–1068.
57. **Spellberg, B. J., S. G. Filler, and J. E. Edwards, Jr.**2006. Current treatment strategies for disseminated candidiasis. Clin. Infect. Dis. **42:**244–251.
58. **Vos, M. C., H. P. Endtz, D. Horst-Kreft, J. Doorduijn, E. Lugtenburg, H. A. Verbrugh, B. Löwenberg, S. de Marie, C. vanPelt, and A. van Belkum.** 2006. *Candida krusei* transmission among hematology patients resolved by adapted antifungal prophylaxis and infection control measures. J. Clin. Microbiol. **44:**1111–1114.
59. **Westbrook, S. D., W. R. Kirkpatrick, C. O. Freytes, J. J. Toro, S. Bernado, T. F. Patterson, S. W. Redding, and S. A. Lee.** 2007. *Candida krusei* sepsis secondary to oral colonization in a hemopoietic stem cell transplant recipient. Med. Mycol. **45:**187–190.
60. **Wingard, J. R.** 1995. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. Clin. Infect. Dis. **20:**115–125.
61. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, T. R. Johnson, J. E. Karp, and R. Saral.** 1991. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N. Engl. J. Med. **325:**1274–1277.